Repopulation: is it inevitably?

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Abstract

A mathematical model of radiotherapy is proposed. The study used the classical 24 hours way of fractionation with a weekend pause. We introduce the matrices of "radiotherapy" and "growth". We developed an equation of the fraction cell evolution, which we solved numerically. The results indicate that the accelerated growth of cells occurs due to the decrease of the fraction of slowly growing cells and increase of the cells that are fast growing.

Repopulation is a serious problem in cancer radiotherapy. The growth of tumor in final stage of radiation can prevent the healing of a patient. Many studies have shown the importance of timing in radiotherapy [2]. If there is a delay in the treatment caused e.g. by interrupts in radiation then this the increases time given to cells for accelerated growth. It was shown that breaks in radiation especially after fourth weeks of treatment lead to the worse results, approximately 2–4.8 percent growth per day of delay.

Why such a strange phenomenon occurs? Tumor fights for its live and it behaves according to the Lenz rule: the lower number of cells the faster the growth. According to Trott [3] accelerated repopulation occurs when the number of cells in tumor decreases below 1000 cells. It can be explained in a few different ways.

Referring to a recent study there [4] are three theories for explaining reasons for repopulations:

1. Fowler model, in which the author claims that cancer volume doubling time T_d approaches potential time T_{pot} as a result of loosing cells.

2. Jones Model which proposes the following explanation: the tumor possesses subpopulations of cells growing with different velocities (speeds); cells are dying equally but those dividing faster gain advantage during breaks in radiation.

3. Trott–Kummermehr model which can be called Dragon Theory. Like a mediewal knight cutting dragon's head have met next two new heads, here stem cells switch from asymmetrical division to symmetrical one. At each division from one stem cell two are arising.

1 Assumptions

We assume as a basis the Jones model.Cancer tumor is heterogenic; it means that there exists fractions of cells that differ in terms of access to oxygen or nutrition or number of mutations.We assume there are three fractions of cells in the tumor, which we will denote:

x_0 – small number of mutations and low growth velocity

x_1 – intermediate number of mutations and medium growth velocity

x_2 – large number of mutations and fastest growth velocity

where these variables are normalized by

$$\sum_{i=0}^{2} x_i = 1$$

In individual fractions there is a well determined number of cell, where

y_i number of cells belonging to the i-th fraction

$$\sum_{i=1}^{3} y_i = N$$

and where N is a total number of cells.

One of mutation factors is the radiation itself [1]. There is no reason to prevent such a phenomenon during radiation. Subsequently to the radiation of tumor after each consecutive dose, the number of cells in tumor will decrease and cells in each individual fraction will undergo mutations. Below is a new model of decreasing of number of cells in each fraction.

Fraction x_i^0 can be expressed by

$$x_i^0 = y_i^0/N \tag{1}$$

Growth of tumor is a result of growth of individual fractions of tumor cells. Each fraction $x_0^0,\ x_1^0,\ x_2^0$ grows with its own velocity $v_0,\ v_1,\ v_2$. Time of duplication of tumor $T_{d,i}$ determines the velocity according to:

$$v_i = \frac{\ln(2)}{T_{d,i}} \tag{2}$$

where $T_{d,i}$ is volume doubling time for individual fraction tumor.There is besides velocity the influence on the tumor growth,on the number of cells in the particular fractions of the tumor. Average velocity of the tumor growth can be described by means of the formula:

$$\Phi = \sum_{i=0}^{2} v_i x_i \tag{3}$$

2 Matrix of radiation

The decrease of the tumor volume, i.e. waste of stem cells is described by the linear – quadratic formula:

$$N = N_0 e^{-\alpha d - \beta d^2} \tag{4}$$

where N is the number of survive cells that radiotherapy , and N_0 is the initial number of cells. Another form of this formula is following:

$$S = e^{-\alpha d - \beta d^2} \tag{5}$$

where S is fraction of surviving cells, α, β are coefficients, d is a radiation dose. Accordingly

$$S = N/N_0 \tag{6}$$

or

$$S = \sum_i x_i^1 \qquad\qquad 1 = \sum_i x_0^i \tag{7}$$

Here x_i^0 are initial fractions before radiotherapy and x_i^1 after first dose of radiation.

$$\sum_i x_i^1 = \sum_i x_i^0 e^{-\alpha d - \beta d^2} \tag{8}$$

When move from fractions to the number of cells then the equations take the form:

$$y_0^1 = y_0^0 (e^{-(\alpha d + \beta d^2)}) \tag{9}$$
$$y_1^1 = y_1^0 e^{-(\alpha d + \beta d^2)} \tag{10}$$
$$y_2^1 = y_2^0 e^{-(\alpha d + \beta d^2)} \tag{11}$$

In matrix notation we have:

$$\begin{pmatrix} y_0^1 \\ y_1^1 \\ y_2^1 \end{pmatrix} = \begin{pmatrix} e^{-\alpha d - \beta d^2} & 0 & 0 \\ 0 & e^{-\alpha d - \beta d^2} & 0 \\ 0 & 0 & e^{-\alpha d - \beta d^2} \end{pmatrix} \begin{pmatrix} y_0^0 \\ y_1^0 \\ y_2^0 \end{pmatrix} \tag{12}$$

The matrix is diagonal and it shows that each fraction decreases according to the linear-quadratic formula and there is no exchange of cells between individual fractions.

This description suggests that all cells behave the same way and are equally sensitive to the absorbed dose gained by the tumor. Investigations show that cancer tumor does not possess uniform cells the individual cells differ in access to the oxygen or nutritious means. One of mutation factors is the ion radiation. During radiation surviving cells inherit improved conditions of oxygenations and nutrition and are undergoing rapid mutation. All these changes lead both to the decrease in the number of cells in individual fractions and also to the change of the proportions of individual fractions. We introduce coefficients Q and P to describe the probability that the cells from fractions x_0^0, x_1^0 will shift to fraction x_1^0 and x_2^0, respectively.

Equation describing this process have the following form:

$$\begin{aligned} y_0^1 &= y_0^0(e^{-\alpha d-\beta d^2}-Q) && (13)\\ y_1^1 &= y_1^0(e^{-\alpha d-\beta d^2}-P)+Qy_0^0 && (14)\\ y_2^1 &= y_2^0 e^{-\alpha d-\beta d^2}+Py_1^0 && (15)\\ & && (16) \end{aligned}$$

Situation after n steps is described by the following equations:

$$\begin{aligned} y_0^{(n)} &= \left(e^{-(\alpha d+\beta d^2)}-Q)\right)\ \ y_0^{(n-1)} && (17)\\ y_1^{(n)} &= Qy_0^{(n-1)}+\left(e^{-(\alpha d+\beta d^2)}-P)\right)y_1^{(n-1)} && (18)\\ y_2^{(n)} &= P(y_1^{(n-1)}+y_2^{(n-1)}e^{-(\alpha d+\beta d^2)} && (19)\\ & && (20) \end{aligned}$$

or in matrix notation:

$$\begin{pmatrix} y_0^{(n)}\\ y_1^{(n)}\\ y_2^{(n)} \end{pmatrix} = \begin{pmatrix} e^{-\alpha d-\beta d^2}-Q & 0 & 0\\ Q & e^{-\alpha d-\beta d^2}-P & 0\\ 0 & P & e^{-\alpha d-\beta d^2} \end{pmatrix}^n \begin{pmatrix} y_0^0\\ y_1^0\\ y_2^0 \end{pmatrix} \qquad (21)$$

We will call the matrix appearing above a radiation matrix and we will denote it $\mathcal{R}$:

$$\mathcal{R} = \begin{pmatrix} e^{-\alpha d-\beta d^2}-Q & 0 & 0\\ Q & e^{-\alpha d-\beta d^2}-P & 0\\ 0 & P & e^{-\alpha d-\beta d^2} \end{pmatrix}^{\backslash} \qquad (22)$$

It can be shown by induction that for each n after summing up rows we obtain following equations:

$$N = N_0\ e^{-n(\alpha d+\beta d^2)} \qquad (23)$$

It means that the matrix $\mathcal{R}$ describes the diminishment of tumor cells after radiation according to the linear quadratic form. Additionally it shows how individual fractions change in time during radiation. Coefficients Q and P allows exchange of cells between individual fractions.

Inserting here values for $\alpha,\ \beta,\ P,\ Q$ the number of cells N and values of fractions $x_0,\ x_1$ we can calculate the rate of decrease of the number of cells in each fraction. From computer simulations it follows that the vector (x_1, x_2, x_3) tends to the equilibrium state $(0, 0, x_2)$. From this we conclude, that radiation of the tumor leads to the selection of cells which are the most mutated and which grow with the largest speed. In the limit of large n this equation has the form:

$$\Phi = v_2 x_2^{(n)}$$

It means that speed of tumor growth is larger when the tumor diminishes, and this effect cannot be avoided.

3 The growth matrix

We describe the rate of tumor growth according to the Sole [5]. We make use of the results of the paper [5] in which it was shown that the equations for growth of the cell fractions can be written as:

$$\begin{aligned}
\frac{dx_0}{dt} &= v_0 x_0(1-Q') - x_0\Phi(x_0,x_1,x_2) \\
\frac{dx_1}{dt} &= v_1 x_1(1-P') + v_0 x_0 Q' - x_1\Phi(x_0,x_1,x_2) \\
\frac{dx_2}{dt} &= v_2 x_2 + v_1 x_1 P' - x_2\Phi(x_0,x_1,x_2)
\end{aligned}$$

or in the matrix notation:

$$\dot{\overrightarrow{x}} = \mathcal{M}\overrightarrow{x} \tag{24}$$

where $\dot{\overrightarrow{x}}$ is the time derivative of the $\overrightarrow{x} = (x_1, x_2, x_3)^T$, $\mathbf{1}$ is the identity matrix and mixing matrix $\mathcal{M}$ is given by

$$\mathcal{M} = \begin{pmatrix} f_0(1-Q') - \Phi(x_0,x_1,x_2) & 0 & 0 \\ f_0 Q' & f_1(1-P') - \Phi(x_0,x_1,x_2) & 0 \\ 0 & f_1 P' & f_2 - \Phi(x_0,x_1,x_2) \end{pmatrix}. \tag{25}$$

and we denote this matrix $\mathcal{M}$ as the growth matrix. Equations of Sole describe how ratios of fractions are changing during radiotherapy. However growth of the cell number in each fraction which occurs during the pauses in radiotherapy we obtain through the following procedure: The result of the Sole equation expressed in fractions x_i we convert to the integer valued number of cells y_i (see below). Obtained number of cells we multiply by factor $e^{ln(2)*v_i} = 2^{v_i}$ and next we pass from the number of cells back to fractions:

$$\begin{pmatrix} y_0' \\ y_1' \\ y_2' \end{pmatrix} = \begin{pmatrix} 2^{v_0} & 0 & 0 \\ 0 & 2^{v_1} & 0 \\ 0 & 0 & 2^{v_2} \end{pmatrix} \begin{pmatrix} y_0 \\ y_1 \\ y_2 \end{pmatrix} \tag{26}$$

Here y_i' is the number of cells after division during pause between consecutive pulses of radiotherapy. Let

$$\mathcal{D} = \begin{pmatrix} 2^{v_0} & 0 & 0 \\ 0 & 2^{v_1} & 0 \\ 0 & 0 & 2^{v_2} \end{pmatrix} \tag{27}$$

denote the division matrix. The growth matrix we construct from mixing and division in the following way:

$$\mathcal{G}(y_i, x_i) = \mathcal{D}(y_i)\mathcal{M}(x_i) \tag{28}$$

We introduce the dependence of v_2 on v_1:

$$v_2 = a v_1 \psi(\theta, Q, P, Q', P', d, n). \tag{29}$$

where

$$\psi(\theta, Q, P, Q', P', d, n) = e^{\Theta - n(\sqrt{Q^2+P^2}d + \sqrt{Q'^2+P'^2}d^2} \tag{30}$$

This form is for radiation period, during weekend the form is different:

$$\psi(\theta, Q', P', d, n) = e^{\Theta - n(\sqrt{Q'^2+P'^2}} \tag{31}$$

It contains a threshold after crossing this threshold velocity v_2 decreases, in accordance velocity Φ also diminishes. In the paper by Sole at al [5] it is shown for which parameters Q', P', M' the fraction x_2 exists.

4 The radiation

The act of radiation consists of:

a. time of radiation — pulse radiation

b. time between consecutive exposures

These equations describe growth of tumor from the moment of ending of radiation till the next exposures. In classical fraction this time is 24 hours. The radiation lasts for a very short period of time: a few minutes, in comparison to 24 hour waiting period between consecutive fractions. Exposition after Wheldon [6] we can call pulse radiotherapy. In the remaining time, tumor cells repair damage from radiotherapy and they divide. The tumor growth appears.

In classical radiotherapy we radiate once a day during the 4-7 weeks, depending on the radiation dose quantity. Duration of radiation is very short (a few minutes), remaining time is spent on the repair of post-radiation damage. Symbolically we can demonstrate this in the following form:

$$\begin{aligned}(growth\ radiation)^5 growth^2 \dots growth^2 (growth\ radiation)^5 |N_0> = \\ ((growth\ radiation)^5)(growth^2(growth\ radiation)^5)^{n-1}|N_0>\end{aligned}$$

where n is the number of weeks of radiotherapy and N_0 is initial number of tumor cells, i.e. $|N_0> = |initial\ number\ of\ tumor\ cells\ >$

Radiation is represented by the matrix:

$$\mathcal{R} = \begin{pmatrix} e^{-\alpha d - \beta d^2} - Q & 0 & 0 \\ Q & e^{-\alpha d - \beta d^2} - P & 0 \\ 0 & P & e^{-\alpha d - \beta d^2} \end{pmatrix} \tag{32}$$

and

$$\mathcal{M} = \begin{pmatrix} f_0(1-Q') - \Phi(x_0, x_1, x_2) & 0 & 0 \\ f_0 Q' & f_1(1-P') - \Phi(x_0, x_1, x_2) & 0 \\ 0 & f_1 P' & f_2 - \Phi(x_0, x_1, x_2) \end{pmatrix}. \tag{33}$$

The radiation process can be described by the following equation:

$$y^{(n+1)} = \mathcal{R}y^n \tag{34}$$

This equation describes the diminishing of the number of cells in fractions after a pulse of radiation. Next we can write the equation which describe the rise of tumor until next exposition. First we describe the change in proportion in fractions in tumor cells. To this aim we change the variable from y to x. We assume that the proportion of $y(t + \text{next day})/y(t)$ is the same as normalized variables:

$$\frac{y(t + \text{next day})}{y(t)} = \frac{x(t + \text{next day})}{x(t)} \tag{35}$$

The Sole equations describe change of proportion during growth of tumor between expositions:

$$\frac{dx^{n+1}}{dt} = \mathcal{M}x^n \tag{36}$$

Differential equations were solved on the interval of one working day and on the interval of three days during weekend.We change solutions of this equation again into the number of cells.Then we calculate how many new cells arise during the pause between radiations. We again pass from x back to y as before and we use following equation:

$$\overrightarrow{y}^{n+1} = \mathcal{V}\overrightarrow{y}^{n+1} \tag{37}$$

We repeat this procedure during prescribed cure time expressed in weeks.

5 Results

We performed numerical calculations for two different sets of parameters: in the first case the probability coefficients of Q, P, Q', P' were zero, in the second they were different from zero and were $Q = 0.0005, P = 0.0005, Q' - 0.1, P' = 0.1$. We took the parameters $\alpha = 0.2, \beta = 0.02, d = 2Gy, n = 30, v_0 = 0.01, v_1 = 0.016$. v_2 was calculated from the formula **??** for $m = 5$ and threshold $\theta = 0.005$. At Q, P, Q', P' equal zero velocity of growth rising of tumor was initially slower, and next faster. The conclusion is simply: the fact of existence of the population of cells of with different growth rates is sufficient for the tumor to grow faster as the corollary of the radiation and intervals between the fraction radiotherapy. At this point the faster growing cells are gaining the population dominance over the slower growing cells and finally lead to the accelerated growth tumor. After introduction the P, Q, Q', P' different from zero the velocity of the tumor growth was also larger. According to this model probabilities Q, P, Q', P' are responsible for the velocity change via the change of the cell population x from x_0 and x_1 to x_2. Fraction x_2 is the fastest growing. Biologically it can be explained that fraction x_2 gains the best condition for growth due to the improvement of oxygenation and better nutrition. Additionally fraction x_2 is built from the most undifferentiated cells and most mutated

cells. The factor that causes the decrease fractions x_0 and x_1 and increase of the fraction x_2 is the radiotherapy which leads to the death of cells and simultaneously by causing the shift of mutation from x_0 and x_1 to x_2. In this way additional radiation influence leads to some differences between situation when the ionization energy is the cause of destroying only cells in fractions ($Q = 0, P = 0, Q' = 0, P' = 0$) and leads to the shift of cells from one fraction to another ($Q \neq 0, P \neq 0, Q' \neq 0, P' \neq 0$). These differences can be seen after subtraction of two graph, see Figs. 1 and 2. In this way we can see how the change of the oxygenation, better nutrition and mutation influence growth velocity. According to the assumption about the existence of the threshold Θ the influence of the coefficients ($Q \neq 0, P \neq 0, Q' \neq 0, P' \neq 0$)is as following: In the first stage we see that they accelerate tumor growth and next they cause the slowing down of the tumor growth. On this example we see a new mechanism leading to the death of the tumor. Namely the existence of the Θ threshold, Namely the existence of the theta threshold, causes that growth mutacji not only shifts cells to faster growing fraction but also crossing sufficient threshold causes slower growth of tumor.

6 Conclusions

Our model explains accelerated growth tumor according to Jones model. The existence of cells fraction of different growth velocity is the cause of the accelerated growth tumor. During the radiation therapy because of the interrupts, cells have time to take advantage of the differences in the velocities of growth and increase the number of cells in fastest growing fraction. In the course of radiation the living conditions of cells are changing: the oxygenation and nutrition is better and additionally mutations appear. Together these factors causes the change of the number of cells in the particular fractions. We have described these changes by the coefficients P and Q responsible for the changes during the radiation pulse and coefficients Q', P' responsible for the changes occurring between different fractions. These coefficients are modifying the tumor growth: in the beginning they accelerate and after crossing the threshold Θ they slow down. The existence of the threshold Θ could explain the benefits from the simultaneous radiochemotherapy. Chemotherapy has the mutagen function. This mechanism in conjunction with radiotherapy facilitates the crossing of the threshold Θ after which the tumor growth is slowing down. From the model it follows that natural state of the tumor is the state described by the vector $(0, 0, 1)$, it means that it tends to the fastest fraction. The fastest and least differentiated fraction gains the crucial dominance. It seems to be in accordance with the clinical experience that often the revival of the tumor is more malicious and less differentiated.

Model that we introduced is the enlargement of the linear–quadratic model. When we take into account only total number of cells it describes the diminishing of the cells tumor exactly the same way as the linear–quadratic model. However it allows to see how the numbers of cells in each fractions change during the radiation and which influence on the velocity of the tumor growth is the appearance of the threshold Θ mutation.

It is possible to apply our model to arbitrary doses, time of radiation and breaks in radiations time.

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Table I

day	fraction 1	fraction 2	fraction 3	velocity
1	371270035	210386353	37127004	0.000000000
1	371476229	212652573	41821898	0.016515136
2	229863321	131585880	25878696	0.016515136
2	229878511	132938244	29136931	0.017018336
3	142245005	82259977	18029449	0.017018336
3	142177843	83060670	20288506	0.017571932
4	87977288	51396563	12554190	0.017571932
4	87883740	51866147	14118852	0.018180004
5	54380999	32093910	8736511	0.018180004
5	54287929	32366123	9818991	0.018846713
6	53706425	32541035	11729058	0.019269721
7	52629285	32602887	14884639	0.019715495
8	32566127	20174125	9210367	0.019715495
8	32380128	20263716	10310082	0.022962204
9	20036285	12538851	6379707	0.022962204
9	19900781	12581216	7133890	0.024044202
10	12314273	7785047	4414332	0.024044202
10	12217058	7802451	4930553	0.025208646
11	7559712	4828027	3050944	0.025208646
11	7490861	4832904	3403560	0.026457045
12	4635221	2990521	2106067	0.026457045
12	4587001	2989628	2346407	0.027789957
13	4457412	2952492	2753154	0.028616727
14	4249783	2878036	3399291	0.029472506
15	2629695	1780881	2103425	0.029472506
15	2583253	1767292	2326276	0.035259776
16	1598474	1093571	1439461	0.035259776
16	1567496	1083328	1589182	0.037028960
17	969941	670345	983359	0.037028960
17	949425	662867	1083679	0.038852571
18	587489	410171	670562	0.038852571
18	573996	404843	737601	0.040720840
19	355179	250510	456415	0.040720840
19	346366	246788	501095	0.042622914
20	326744	236600	570777	0.043757469
21	297833	220498	673761	0.044897230
22	184294	136440	416912	0.044897230
22	178080	133186	453545	0.051789508
23	110193	82413	280646	0.051789508
23	106278	80297	304735	0.053649548

day	fraction 1	fraction 2	fraction 3	velocity
24	65763	49686	188565	0.053649548
24	63311	48322	204376	0.055462791
25	39176	29901	126465	0.055462791
25	37648	29028	136826	0.057219673
26	23296	17962	84665	0.057219673
26	22349	17408	91445	0.058911922
27	20408	16155	100824	0.059878183
28	17720	14341	113371	0.060818297
29	10965	8874	70152	0.060818297
29	10444	8539	75231	0.065925766
30	6463	5284	46552	0.065925766
30	6148	5078	49860	0.067155054
31	3805	3142	30853	0.067155054
31	3615	3017	33006	0.068300215
32	2237	1867	20424	0.068300215
32	2123	1790	21826	0.069362910
33	1314	1108	13506	0.069362910
33	1246	1061	14418	0.070345563
34	1112	962	15538	0.070889546
35	934	826	16893	0.071407364
36	578	511	10453	0.071407364
36	546	488	11117	0.074038283
37	338	302	6879	0.074038283
37	319	288	7312	0.074629103
38	197	178	4524	0.074629103
38	186	170	4806	0.075165861
39	115	105	2974	0.075165861
39	109	100	3158	0.075652632
40	67	62	1954	0.075652632
40	63	59	2074	0.076093354
41	56	53	2209	0.076333559
42	46	45	2362	0.076559766
43	29	28	1461	0.076559766
43	27	26	1548	0.077673641
44	17	16	958	0.077673641
44	16	15	1015	0.077915957
45	10	10	628	0.077915957
45	9	9	665	0.078133711
46	6	6	412	0.078133711
46	5	5	436	0.078329254
47	3	3	270	0.078329254
47	3	3	285	0.078504740
48	3	3	303	0.078599769

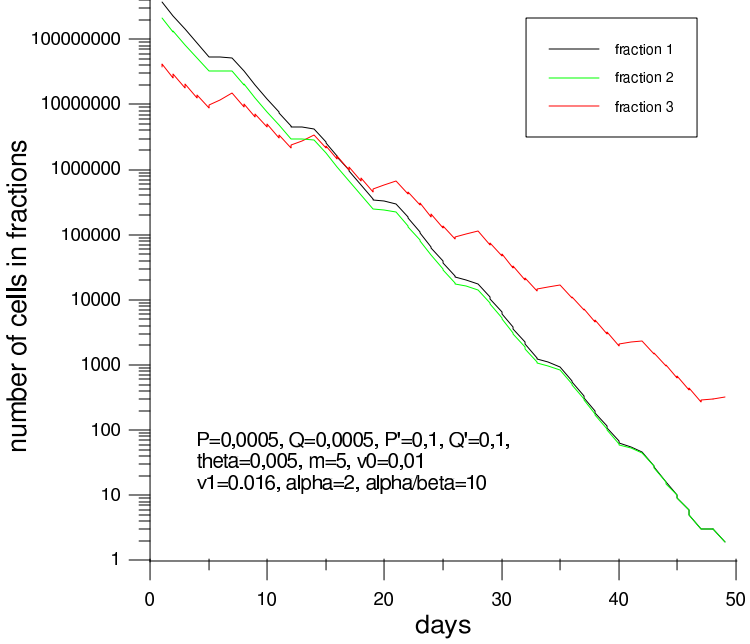

Figure 1: Plot of velocity of the tumor growth as a function of time (days) of radiotherapy. Here Q, P, Q', P' are zero.

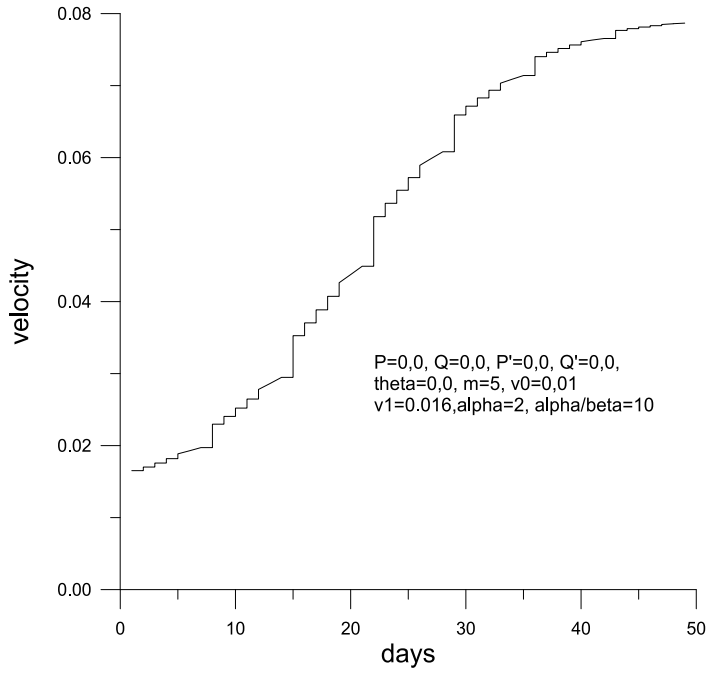

Figure 2: Plot of velocity of the tumor growth as a function of time (days) of radiotherapy. Here Q, P, Q', P' are different from zero.

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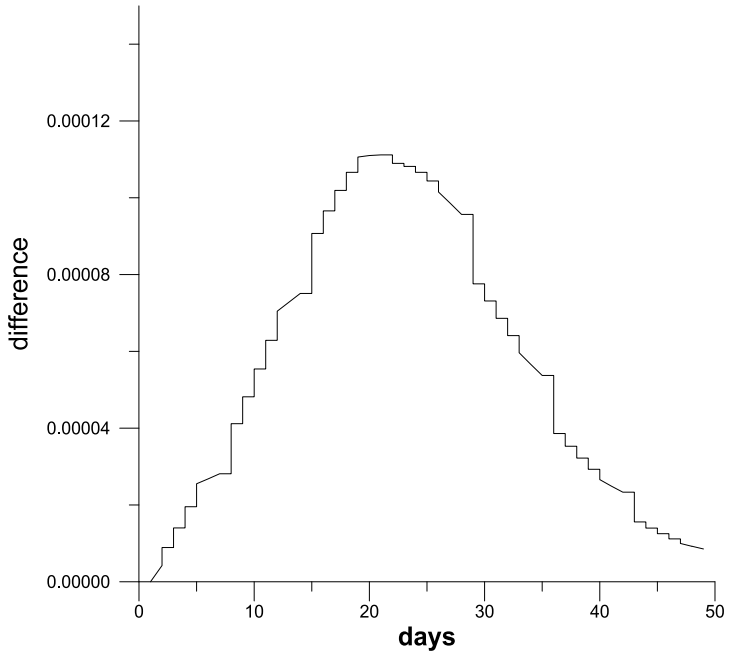

Figure 3: Plot of velocity for zero valued parameters subtracted from velocity for parameters different from zero.